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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | | ATTORNEY DOCKET NO. |
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| 08/486,313 | 06/07/95 | WEISS | S | A-61105-11/D |

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| EXAMINER | |
|---|---|
| BAKER, A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 45 |

**DATE MAILED:** 01/31/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/486,313 | WEISS ET AL. | |
| | Examiner | Art Unit | |
| | Anne M. Baker | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *26,27,32-37 and 39-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27,32-37 and 39-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *07 June 1995* is: a)☐ approved b)☒ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

The response filed November 9, 2000 (Paper No. 43) has been entered.

Claims 26, 27, 32-37, and 39-62 are pending in the instant application.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

### *Transitional After Final Practice*

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on November 9, 2000 has been entered.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 27, 32-37, and 39-62 stand rejected under 35 U.S.C. 112, first paragraph for reasons of record advanced in the previous Office Action mailed 10/12/99 (Paper No. 36), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of transplanting neural stem cell progeny into a host by obtaining a population of cells derived from mammalian neural tissue containing at least one multipotent CNS neural stem cell, where the neural stem cell produces progeny that differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or galactocerebroside; culturing the neural stem cells in a culture medium containing one or more growth factors that induce multipotent neural stem cell proliferation; inducing proliferation of multipotent neural stem cells to produce progeny which includes multipotent neural stem cell progeny cells and transplanting said multipotent neural stem cell progeny into the host.

The claims are not enabled because the transplantation of multipotent neural stem cell progeny into a host has not been demonstrated to provide any therapeutic benefit to the host. The specification clearly teaches that the only use for the transplant method is to produce a therapeutic effect in the host.

Applicants assert that they have demonstrated a therapeutic benefit and specifically, that Applicants have provided evidence demonstrating that, after the cells are transplanted, a therapeutic benefit may be provided. In support of this assertion, Applicants state that, after transplantation, the cells actively secrete cellular products, such as peptides. Applicants further state that the cells differentiate *in vivo* after transplantation into tissue-environment appropriate cell lineages that may replace diseased or damaged tissue or may repair such tissues. Applicants offer a declaration as evidence for these cellular activities.

The Declaration of Dr. Joseph P. Hammang (hereinafter referred to as "the Declaration") has been fully considered but is not deemed persuasive. The Declaration states, in paragraph 7, that the specification provided working examples at pages 96-101, of neural stem cell transplantation in various disease models, including Huntington's disease, Parkinson's disease, and cardiac arrest. However, no therapeutic effect

resulted from the transplantation. These examples have already been addressed on pages 3-4 of the Office Action of Paper No. 29 (mailed 1/21/99).

The Declaration states that the transplanted cells secrete cellular products and that, upon transplantation, tissue-specific differentiation occurs *in vivo*. The declarant therefore concludes that transplantation of neural stem cells would have a reasonable expectation of success in providing a therapeutic benefit to the host. However, the specification does not offer specific guidance for using these properties to produce a therapeutic effect using the claimed methods of transplantation. Ample reasons have been provided on pages 3-5 of the Office Action of Paper No. 29 to doubt that the method taught could be used without additional manipulations or without identifying special conditions under which the method could be used to produce a therapeutic effect.

The declarant argues that because CNS neural stem cells (NSCs) form myelinating oligodendrocytes *in vivo* in dysmyelinated environments, that NSCs would be useful in providing a therapeutic benefit to the host. However, the instant specification does not provide all of the steps, or the specific conditions under which transplantation can be performed to produce myelinating oligodendrocytes which then function to produce a therapeutic effect. In the absence of teachings sufficient to allow the skilled artisan to produce a therapeutic effect using the claimed method, one skilled in the art would not how to use the claimed method.

The declarant states that Milward et al. (1997) successfully transplanted canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The declarant further points out that Milward et al. report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. The declarant concludes that these result demonstrates that CNS NSCs can be used to therapeutically provide myelin to recipients. However, the formation of myelin, as described by Milward et al., did not result in producing a therapeutic effect in the animal. Thus, Milward et

al. does not demonstrate application of the claimed method to produce a therapeutic effect. This art has already been addressed at page 5 of Paper No. 36.

The declarant states that Zhang et al. (1999) report producing "robust myelination" in myelin-deficient rats upon transplantation of neural stem cells. The declarant concludes that this result demonstrates that transplantation of NSCs "would be useful in providing a therapeutic benefit to the host." However, this "robust myelination" in fact did **not** produce a therapeutic effect in the host.

The declarant points to Brustle et al. (1998) for describing the implantation of fetal human CNS progenitor cells into mice. Upon transplantation the cells "acquire an oligodendroglial phenotype and participate in the myelination of host axons." The declarant again concludes that these results demonstrate that transplantation of NSCs "would be useful in providing a therapeutic benefit to the host." However, these experiments were carried out in healthy animals. Thus, no therapeutic effect was demonstrated. The function of the cells upon transplantation is not sufficient to support enablement because there is not sufficient guidance for using the transplantation method therapeutically in diseased animals.

The declarant states that Yandava et al. (1999) demonstrate a therapeutic effect upon transplantation, wherein transplantation of CNS NSCs resulted in "global" cell replacement and therapeutically effective remyelination in mice. The declarant points out that NSCs transplanted at birth resulted in widespread engraftment throughout the dysmyelinated shiverer (*shi*) mouse brain with repletion of myelin basic protein. The declarant points out that a number of recipient animals showed a decrease in symptomatic tremor. This art has already been addressed at page 6 of Paper No. 36. While some therapeutic effect was seen, in so far as a number of recipient animals showed a decline in symptomatic tremor, the method of transplantation used a cloned cell lined from neonatal mouse cerebellum (p. 7030, column 1, paragraph 3). This clone was not derived in the same manner as is taught in the specification for isolating neural stem cells. Thus, as the

reference does not use the neural stem cells as recited in the claims, it does not support enablement for the claimed methods. Applicants have not addressed this issue.

The declarant states that Flax et al. (1998) showed that transplantation of CNS NSCs provides a therapeutic benefit in the meander tail (*mea*) mouse, a mouse mutant model characterized by a cell-autonomous failure of granule neurons to develop or survive in the cerebellum. Flax et al. transplanted human CNS NSCs into newborn mea cerebella and confirmed that the human NSCs provided "replacement neurons" with the "definitive size, morphology, and location of cerebellar granule neurons. The declarant concludes that the provision of replacement neurons is evidence of a therapeutic benefit upon transplantation. However, these "replacement neurons" in fact did not produce a therapeutic effect. Thus, it is unclear how the claimed method can be used for therapy, since no teachings are provided to allow the skilled artisan to produce "replacement neurons" for therapy.

The declarant states that Fricker et al. (1999) teach that NSCs migrate to the desired target and differentiate into the appropriate lineage. Thus, Fricker et al. demonstrate the ability of human NSCs to respond *in vivo* to guidance cues and signals that can direct their differentiation. The declarant concludes that Fricker et al. demonstrates that transplantation of NSCs "would be useful in providing a therapeutic benefit to the host." However, this property of NSCs has not as yet been exploited to develop methodology to produce a therapeutic effect. The steps required to produce a therapeutic effect for any given deficit are not known, and neither the specification nor the art teaches how to do this without undue experimentation.

The declarant states that Aboody et al. (2000) states that NSCs provide a transplantation "platform" since upon transplantation those cells can continue to express a foreign gene and migrate in a site-specific fashion in host tissue. The declarant concludes that Aboody et al. demonstrates that transplantation of NSCs "would be useful in providing a therapeutic benefit to the host." Again, Aboody et al. does not teach the

steps required to transplant NSCs in a manner such that a therapeutic effect is produced. Thus, while the development of methodology for therapeutic transplantation is still being studied, one skilled in the art would not be able to practice the claimed method without undue experimentation. The cited references are evidence that further research is being conducted to develop methodology for therapeutic transplantation and to study the function of NSCs *in vivo*, but the steps required to produce a therapeutic effect for any given deficit and the conditions under which therapeutic transplantation can be successfully performed have yet to be determined.

Functional studies are not sufficient to support enablement of the claimed method because the specification does not provide specific guidance for producing a therapeutic effect without undue experimentation.

Thus, for all the work that has been done to study the function of these cells upon transplantation, the art has not, as yet, found a way to use the cells therapeutically in transplantation.

***Conclusion***

No claim is allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.129(a) and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.129(a). Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the submission under 37 CFR 1.129(a). See MPEP 706.07(b). Applicant is reminded of the extension of time policy set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

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